product and inject large volumes, which also not everybody likes. So, I think that 95 percent is probably the reasonable amount, and as a number of people pointed out, there is no clinical data to point out that there is a problem at that level.

Well, 90 may be a bit too low, but it is traditionally level, and there is a big body of data that we had analyzed or the agency had analyzed and concluded that the drug is safe and effective, whereas, it was produced under the 90 percent limits.

DR. KASLIWAL: Do you know what concentration you think the stability problems have?

MR. KISELEV: The stability problem starts at the concentration exceeding about 100 millicurie per mL. In order to make the FDG a truly clinically useful drug and make it available to the wide patient population, I think they are shooting at concentrations in excess of 200 for logical in distribution, logical and cost effective distribution.

MR. SWANSON: Also, correct me if I am wrong, doesn't the drug have to meet its acceptance criteria throughout its expiry period?

DR. KASLIWAL: That's right.

MR. SWANSON: So, then you are dealing with a radiochemical impurity of 0.25 percent at time of

calibration in order to maintain it below 2 percent throughout an eight-hour expiration period? Pretty difficult to achieve.

DR. KASLIWAL: Maybe the solution is when you get to very high radioconcentrations, you have to use stabilizer, who knows.

DR. CONTI: Again, the experience is such that at the concentrations that we have been traditionally producing these isotopes at, which is below this level, at the 90 percent radiochemical purity level, it has not interfered with the clinical utility of the test, so I would encourage you to focus on that piece of information as the baseline.

If someone goes to an extreme, then, they would be then required to document issues, such as stability or the impracticality of doing a scan with that level of contamination.

MR. WATKINS: I have a comment. My name is Len Watkins from the University of Iowa.

We have done quite extensive studies in this area, as well. We don't make by far the amounts that Maxim uses, but with a 500, 600 millicurie batch in 18 mL, we get most of the time zero percent fluoride in our product when we start.

I have taken samples throughout the day. Whenever we inject a patient, I have taken a sample at the same time

and measured it. As the day goes along, we see increasing amounts of fluoride, usually not exceeding 2 percent, but the higher amount of activity you start off with, the more radiolytic the composition we have.

I have asked the physicians who read the scans to tell me if they see any difference during the, and we have done I would guess probably 100 or more, and the physicians have never reported back that they have seen any difference in the scans between the early part of the day and the late part of the day.

MS. AXELRAD: We hear your comment. I think we will have to look into this some more, and we may have further discussions on this.

Do you have other comments?

DR. BARRIO: Yes, on the same page, under pH, when you refer to pH paper and pH reference standards, you are referring to the color scale when you use the pH paper or you are talking about something else?

MS. AXELRAD: Is it page 11?

DR. BARRIO: Page 11 under pH.

MS. KEPPLER: You are talking about the color scale on the box?

DR. BARRIO: pH paper and pH reference standards.

DR. KASLIWAL: No, I was talking about the standards, the pH standards, the drops.

MR. SWANSON: Do you have to do that with each pH test or is that part of your validation of your pH paper?

DR. KASLIWAL: You could probably do it as part of your validation.

DR. LEUTZINGER: I think so. I think you can just validate, doing the validation.

DR. KASLIWAL: The specific paper you are using.

DR. BARRIO: Also, at the bottom, you mean osmolarity, I guess.

Finally, the measure of glucose concentrations, why would anybody like to or would have to calculate the amount of glucose present, who cares really?

DR. KASLIWAL: No, the calculated amount is based on your batch formula. In the batch formula, you are specifying the amount of substrate on that, you can calculate and specify here the maximum amount of glucose present assuming everything hydrolyzes.

DR. CONTI: What is the purpose of knowing how much glucose?

DR. KASLIWAL: That is the description of your product. You have to know what is in your--you know, your definition of the product, what's in the product, and we are not requiring that you need to test it. You need to calculate and just specify there that will be the maximum amount present. It's a calculated amount from the amount

that you use.

DR. CONTI: Dr. Barrio mentioned osmolality, should the correct thing be osmolarity?

DR. KASLIWAL: I thought in the package insert it's osmolality--it's molarity or molality?

DR. CONTI: It's with an "r," it should be with an "r."

DR. KASLIWAL: Okay, whatever is in the package insert. Usually, we have osmolality.

DR. CONTI: It is not really practical to measure osmolality in certain circumstances, so I would suggest you stick with osmolarity, and change the package insert.

MR. MOCK: Do we need to test for the amount of water in the dose? That's an ingredient. If we have to test for glucose, why not water?

DR. KASLIWAL: No, you test for active ingredients or any functional inactive ingredients.

DR. CONTI: Back on page 10, the Appearance, the Procedure, validation, I am wondering what the validation is. It says, "Visual observation under adequate light."

DR. KASLIWAL: What is your question, are you asking what would be the validation for that?

DR. CONTI: Yes.

DR. KASLIWAL: If you look at what we have asked that you submit data, validation data, show suitability--we

haven't asked for that validation data, if you look underneath the analytical procedures.

MR. SWANSON: Under Residual Solvents, the not more than limits are percents. I think percents are independent of total volume.

MS. AXELRAD: Could you give us a page? It is really hard to follow.

MR. SWANSON: I am sorry, page 11, the bottom of the page, Residual Solvents, we have not more than 0.04 percent, 0.5 percent, but we have per volume, and a percent is independent of a total volume measurement, so it doesn't make sense to have per volume there.

DR. KASLIWAL: We will correct it to reflect that.

DR. CALLAHAN: I have a point on the radionuclidic purity on page 11. You talk about gamma spectroscopy of a decayed sample. If it were a completely decayed, would you really have a 511 photon? There is a specification in the USP about radionuclidic purity, which suggests that you do a sample and look at the spectrum, but it doesn't say decayed sample. I know why you do a decayed sample, to look for the long-lived, very low level trace materials, but if you need to look for those, you have no positron emitters left there, so I don't understand this.

I can see doing a radionuclidic purity on an active sample and making sure there is not significant

amounts of something else there, but if you are going to do it on decay, then, the acceptance criteria should be that there is nothing there.

DR. KASLIWAL: I think you are right. The real intent is to decay the sample and see what you have got.

MR. CLANTON: Jeff Clanton, Vanderbilt.

Would it be fair to say that the test for 2-chloro-2-deoxy-glucose could be replaced if you are doing base hydrolysis with a test for the mannose derivative?

DR. KASLIWAL: Right. If you look at the top, if there is no possibility that your method is going to provide an impurity, you don't have to test for it. If you are using a procedure where you cannot form an impurity, for example, if you don't use solvent, you don't have to have a specification for that.

DR. CONTI: Back to radionuclide identify, bottom of page 10, we discussed this last night. We need to make sure that this is alignment with USP because according to my calculations, it is not possible to measure in 10 minutes with 3 percent accuracy this half-life. So, I think we had some other numbers to take a look at.

DR. KASLIWAL: We will make that consistent with USP, no problems.

MR. CHALY: Thomas Shaly from North Shore University Hospital.

I would like to know whether these tests have to be done on each sample or these are validation testings.

DR. KASLIWAL: I think if you look at the testing schedule, it says that.

MR. CHALY: You will appreciate if you don't include that osmolarity testing and the radionuclide testing on a routine basis.

MR. WATKINS: I would like to just return to this osmolality. As far as I know, in the most recent USP there is no mention of measuring osmolality. Is this going to be a separate issue?

There is no requirement as far as I know in the current USP to measure osmolality, and why are we asking to have it here.

DR. BARRIO: It's calculated, I guess. I would have the same question, yes.

DR. CALLAHAN: We just removed the requirement, the word isotonic solution in the description of the drug product in the monograph, so it no longer is defined as an isotonic solution.

MR. SWANSON: A point of clarification. The USP PET compounding guidelines do require you to calculate an osmolarity as part of your initial validation procedures under product, but there is no requirement for you to routinely test for that, and there is no requirement for the

product to be isotonic.

MR. WATKINS: Thank you.

MR. SWANSON: Ravi, a little semantics. On page 3, for example, you have under Name of Target Material, 18 Water, you have test and acceptance criteria. To me, that implies that you have acceptance criteria, and then what tests are you going to perform to ensure the acceptance criteria is met for that component.

That is not really what we are saying we are going to do because basically, you may not have to do all those tests, okay, so I think test is probably an inappropriate word and it probably ought to be something like characteristic and acceptance criteria is what you are saying, because appearance is not a test.

DR. KASLIWAL: Usually, it's test procedure and acceptance criteria. It's not a procedure test identity, and this is the criteria for identity. You have to establish that, and the information for that, you can get it out of COA and make sure that COA data is consistent with your established criteria.

Underneath that section, there is then a section that says, okay, that's fine, but then exactly what would you do to release the product for use. So, in that, whatever it is that you are doing, you need to describe, identity test performed to release each lot for production

use. This is for 18 water.

MR. SWANSON: I think you still miss my point. I don't want somebody that fills this out for a component to think that for each of the stated acceptance criteria, they have to do a test. You know, your test means what is the test you are going to do to evaluate that specific acceptance criteria. Okay.

So, I think there is just probably a better word to use than test there. Okay.

DR. KASLIWAL: Okay.

MS. AXELRAD: Is that it for this one? We have an option. We could either go through specific comments on the other two, or you could just submit them in writing. If you feel there are things that need to be discussed, we can talk about them, but if you--

DR. BARRIO: We probably could go quickly through them, if you don't mind.

MS. AXELRAD: Okay.

MR. KUHS: Before we leave that, on page 8 of the draft procedure, there is operating parameters under high-pressure targets, it is under Operating Parameters, and you have a number of different parameters of the targets that you are using, and those certainly need to be ranges, and the operating pressure often changes during the irradiation cycle, so I don't think that you can say that

there is one specific pressure.

I am not sure why you even distinguish between a high-pressure and a low-pressure target, and without any definitions of what high pressure or low pressure are outside of they are called that, it is really meaningless information.

DR. CONTI: I would also like to consider maybe going more to manufacturer specifications and operating of the devices as opposed to this type of setup.

DR. KASLIWAL: That's fine. What you can then do is just state the manufacturer's specifications in here, what those are.

MS. AXELRAD: Which one are you going to do next?

DR. BARRIO: Sodium fluoride.

DR. CONTI: I actually had a question on this in terms of the issue regarding the source of the F 18 fluoride. There is an inconsistency between the FDG documentation and the sodium fluoride documentation.

In the fluoride documentation, it requires us to list a drug master file for receiving it from another entity, but it doesn't give us the options of if we receive it from a facility that does not have a DMF to go ahead and do the testing for acceptance of the material, just like you would with the FDG.

There is a page here on the FDG, for example, on

page 4, that says, "If yes, provide the following information for the supplier," but that is not an option under the sodium fluoride package.

DR. KASLIWAL: I guess the difference is in FDG, fluoride is a reagent. Here, it is the drug substance itself, and that is a very, very critical difference, and you need to have that additional information in this case. I mean you are buying a drug substance from somebody, and the level of information in that case is more than if you are buying a reagent that you are going to use in a synthesis to make something else.

DR. CONTI: I understand that, so you are eliminating the possibility of us doing an acceptance criteria for using this in patients by requiring us to only get it from a drug master file provided facility.

DR. KASLIWAL: I suppose you can provide the information that is listed there right in this application, but you have to be aware that--the reason we have drug master file is because the drug master file holder has the agreement.

They sign a certification that if they change anything, they will notify you that they changed, which then, in turn, you can notify us. They would also notify the drug master file, so if there is any change, it is to protect you. They don't do it without telling you as the

user of the product.

If you provide the information in your NDA, I suppose you can have an agreement with them.

MS. AXELRAD: You don't have to get it from a drug master file holder, you can supply it yourself, but then you are held accountable if there is any changes that the supplier makes and they don't tell you about it, you are going to be held responsible for knowing about those things, I mean if you provide it directly yourself.

You always have that option. A drug master file is simply a mechanism that the agency has, so that the supplier can keep the information confidential. You can always just get it, they can always give it to you, and then you can incorporate it in your application, and then you can just have an agreement with them that they will tell you whenever they change anything, and then you can submit a supplement to your application to take that into account.

MR. KUHS: Couldn't that information be just delivered with the--we are thinking of, in this case, an occasional use of fluoride from someone else, where they just gave you the parameters that they operated under that particular day, and oftentimes that is available on a printout. They can also give you the parameters under which it was made.

There is also one other assumption that the F 18

is going to be delivered in a solution, and probably that is not true. Most of the time it would be delivered as an ion and an ion column, an ion exchange column.

DR. KASLIWAL: Thank you.

MS. AXELRAD: Ravi, I will have to think about those things and figure out how to incorporate it.

Someone from the audience, go ahead.

MR. MATTMULLER: Hi. I am Steve Mattmuller from Kettering Medical Center in Kettering, Ohio, not to be confused with our small cousins in New York, Sloan Kettering.

In FDA, Section 6, FDG, Manufacture of Drug Product, B. Reprocessing of PET Drug Product, I was curious if we could get some additional information on this and also make sure I am on the right page with you all on this.

I am thinking if, for example, the bubble test fails, that we could reprocess the solutions for a new filter, the new bubble test passes, then, we are okay. Is that what you had in mind for something like that as far as reprocessing?

DR. KASLIWAL: Which drug are you looking at?

MR. MATTMULLER: FDG.

DR. KASLIWAL: And you said what page?

MR. MATTMULLER: I downloaded it from the web. It's page 9 on mine. It might be page 10 of yours, I

believe.

Section 6. Manufacture of Drug Product. Part B, Reprocessing of PET Drug Product.

DR. KASLIWAL: Right. That will be one scenario where you can filter it and be able to use it, but you need to state that under this condition you will do that.

MR. MATTMULLER: Thank you. I am curious. Do you have any other potential reprocessing steps that might be acceptable?

MS. AXELRAD: We welcome you to suggest some to us that we can look at.

MR. MOCK: There are a number of examples of additional reprocessing other than sterility. If the fluoride level is too high, run it through another silica cartridge or a luminar cartridge.

If the intermediate--you question whether that worked--another C 18. The pH wasn't quite right, you know, there is the number of things that can be done, so I don't think you are restricting it to any one particular type of reprocessing. I hope that was not the intent.

MS. AXELRAD: No, it isn't. You can write in here whatever things you--circumstances under which you might want to reprocess, and we will look at it when we look at the application.

DR. KASLIWAL: I think the only issue we may have

with the reprocessing, what you just mentioned, yes, that will get rid of fluoride, but so would probably chloride and other ions, and you would probably change the whole osmolality of the solution.

DR. BARRIO: Not very much.

DR. KASLIWAL: Okay.

DR. BARRIO: Going back to F 18 fluoride, page 7, something very trivial, I guess, under 6A. You mean for each batch of fluoride F 18 injection, right, not FDG?

DR. KASLIWAL: You are right.

DR. BARRIO: Do you guys have any other comment?

MS. KEPPLER: I think it was just the same comments about osmolarity, as well as the radionuclide identity test being in conformance with the USP that we also picked up in this.

MR. SWANSON: In other words, some of the comments we made under FDG would generalize to all of these, and you just need to take a look at those.

DR. BARRIO: Can we go to ammonia then? On page 11, under Radionuclidic Identity, we say yes/yes. It should be yes/no, I believe, because in F 18 fluoride we have yes/no. It should be the same, I believe.

MR. SWANSON: The same thing on that page for osmolality, it would be a calculate. You basically need to go back and make the tables standard.

DR. BARRIO: We discussed yesterday the issue of--let's go to page 8. A specific activity, I think it should not be determined if we are using this procedure--because it is similar to the others.

DR. KASLIWAL: In reading the literature, my understanding you can form actually some ammonia during the radiation, don't you? I mean that is some of the literature, some of them do indicate you actually can.

DR. BARRIO: Are you saying that we are forming--

DR. KASLIWAL: I don't know, that is what the literature says.

DR. BARRIO: Ammonia, mass amount of ammonia?

DR. KASLIWAL: Mass amounts of ammonia. I think there is no way you could do that. There is a possibility of--how can you form ammonia--I don't think there is any way during bombardment you can form ammonia unless you have nitrites and nitrates already in your water, and then during the bombardment conditions and the alcohol present, you can form massive amount of ammonia, but I don't see this as being--you have to remember that we have large amounts of ammonia now in circulation. This is like the glucose issue, it really doesn't matter.

DR. KASLIWAL: I remember reading a procedure that they seemed to state that you could actually form ammonia.

I think it was a no-carrier added where you can't

form, we will probably accept your no carrier added statement there, but if there is a possibility of forming, then, we are going to have to stick with something like that.

DR. BARRIO: Certainly, this is a problem with carbon 11, let's say, CO_2 in which you contaminate or you could contaminate your sample with CO_2 from the atmosphere or whatever, but I don't think that is the case here.

Now, the other issue we discussed yesterday, of course, is in the US monograph, is the limitation for nitrites and nitrates to be 2 percent each. The bottom line is that this probably is relevant where this 2 percent each or 4 percent, 1 and 0 the other, and things like that, but we became a little concerned because the array of chemical impurities stated are 94 percent, and we can reject a batch simply because he has more than 2 percent nitrites or nitrates. This is clearly an inconsequential issue.

One thing we could do is to discuss tomorrow under the USP, I mean during that meeting, but I don't know if you guys have some comments on that, but I think this is not a very important issue.

MR. CHALY: I am Thomas Chaly from North Shore University Hospital.

We have been using N 13 ammonia using the [Dewaters elismotad] for the last 10, 15 years. We haven't

seen any great amount of nitrite or nitrate in our product.

DR. BARRIO: But in the alcohol procedure--

MR. CHALY: We haven't done the alcohol procedure.

DR. BARRIO: Right. But in the alcohol procedure, it depends upon how you do it. You can see a little amount of nitrite and nitrates. Then, some centers will pass ammonia through a column to remove the anions and leave the cations like ammonia go through. That procedure will be mostly affected by this.

MR. CHALY: In the Dewaters process, we are distilling it out completely.

DR. BARRIO: That's right.

MR. CHALY: So, distilling it out, so we are not contaminating--

DR. BARRIO: But with the alcohol procedure, that is a problem.

If you guys don't have any comments, we are very much done here with this except what Dennis has said just to make sure that it is consistent with the others, and thanks very much.

MR. FERRIS: Is the comment period for this document October 13th, as well?

MS. AXELRAD: Yes, I think that we will say the comment period for all of these are October 13th. Furthermore, on that one, which I didn't really get a chance

to look at, it needs to be somehow merged perhaps with the chemistry section. I mean it asks, for example, for the name of the manufacturer, and so does the chemistry section. So, we will square those and try and make sure that all the pieces of this sort of fit together, and you don't have to have redundant information in different sections of the application.

MR. FERRIS: Thank you.

MS. AXELRAD: Let's move on to Clinical Pharmacology/Biopharmaceutics. We just want to briefly alert you to the fact that there is this requirement. We think that it will be fairly easy to deal with in the applications for FDG, ammonia, sodium fluoride. We want to tell you what the requirement is and how we are going to be approaching it.

Clinical Pharmacology/Biopharmaceutics

MR. HUNT: I am John Hunt. I am from the Office of Clinical Pharmacology and Biopharmaceutics. As Jane has indicated, I am going to talk on the area of clinical pharmacology and biopharmaceutics particularly related to the regulatory umbrella we are working under and as related to what kinds of information needs to be provided in an NDA or an ANDA.

I have a four-page handout that I will talk through. On the second page, I have highlighted the section

of the Code of Federal Regulations, particularly Part 320, that addresses the bioavailability and bioequivalence requirements.

Under that part there is a Section 320.21 that states that when a sponsor submits an NDA or an ANDA, they either need to provide in vivo bioavailability data, that relates to the NDA, or bioequivalence data, which relates to an ANDA. Alternatively, you can submit information to allow a waiver for not meeting in vivo bioavailability or bioequivalence information.

This morning we had a lot of discussion on definitions, so I included one here to focus on the term bioavailability. As stated in the regulations, it states that bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

Now, for I.V. products, historically, the agency has assumed that an I.V. product is 100 percent absorbed, so although the definition addresses the percent absorbed concept, we assume that an I.V. is 100 percent absorbed.

Also, in this section of 320, there is a section related to waivers, and there is two scenarios. Particularly for these kinds of products, which are parenteral products, there is one section that says for the drug product, (1) is a parenteral solution intended solely

for administration by injection.

The second component of that requirement for a waiver is that it contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full new drug application. That is the listed reference drug.

There is also another component of the waiver criteria, which is general, for good cause, for the public health. Historically, the agency hasn't really used that when there is the ability to measure something.

On a few occasions, it has been used when there is a critical need to get a product on the market and there is not technological methods available to quantitate a drug in terms of in vivo performance.

In the area of sodium fluoride F 18, there is an approved product, and as Jane indicated, I am guessing that there is going to be procedures worked out where the information about the approved product would be made available.

Since there is only one synthesis procedure method for this agent, and lastly, if there are CMC limits that are set, if a sponsor can meet those three criteria, that is, provide information on the ingredients of their product related to the reference listed drug, that it is identical, again, it's the same synthesis process, and it meets the CMC

specs, then, all that would be needed is citing this section of the regulations and getting a waiver for it. You would not need to do in vivo kinds of studies.

DR. CONTI: The synthesis process for sodium fluoride, the reactor produced versus the cyclotron produced, you are calling equivalent?

DR. KASLIWAL: Where is the reactor produced product?

DR. CONTI: Reactor produced sodium fluoride is what was used years ago, as well as cyclotron produced materials.

DR. KASLIWAL: I think the package inserts say that it is a cyclotron produced product.

DR. HOUN: It does say this solution contains no carrier added fluorine 18 as the fluoride ion in isotonic sodium chloride solution. The 18F is produced by bombardment of neon gas accelerated in a cyclotron.

DR. CONTI: On your documents here, as I recall, it said something about either FDG or fluoride, it says something about reactor produced material. Yes, on page 4 of the FDG, Chemistry, Manufacturing, and Controls document, Item 3 in the lower large box, it talks about reactor produced fluoride.

DR. KASLIWAL: You are looking at FDG.

DR. CONTI: Yes.

DR. KASLIWAL: That is if somebody wants to buy fluoride from a reactor produced product, then, we are going to have additional issues with it, specifically, some radionuclidic impurities.

MS. AXELRAD: So, we are just asking them to let us know if it is reactor produced.

DR. CONTI: But in this document here, I want to make sure I understand, the only way that you can get equivalence is that the material is being compared to the original cyclotron produced material. Okay.

MR. FERRIS: You are saying the same thing is true with spectral lineac, as well?

DR. LEUTZINGER: I don't know about the lineac. We would have to look into that, but I presume that there wouldn't be any--

MR. FERRIS: They are combined in this statement of reactor or lineac.

DR. LEUTZINGER: We would have to look into the lineac, but I would presume--what I know about the lineac, there wouldn't be any reason to suspect anything different than you would in the cyclotron at this point.

DR. CALLAHAN: When you read the package insert there you stated that it was the deuteron on neon reaction, right? That is not the reaction that anyone would use today to make fluoride, I don't believe. There goes the waiver

process.

MS. AXELRAD: Basically, I think that what we are trying to say is that it is very easy if you could show sameness. If you can't show sameness, we are going to have additional issues with it.

Can you explain that, John?

MR. HUNT: We have had a lot of discussion internally that if it isn't identical and what would we consider, and going again back to the regulations, if it doesn't fall under a waiver, then, we need some kind of a study, and one thought is a dosimetry type study, but we are certainly open to any thoughts where you think the appropriateness might be related to that if it can't fall in the window of being a same product as a reference listed drug.

MR. BRESLOW: Ken Breslow, PETNet.

Regarding the criteria under (b)(2), that it contains the same active ingredients in the same concentration as the reference drug, with FDG that is going to be an issue, because the reference product currently is a relatively low specific concentration range, which is probably lower than most distributors would require to produce.

Here again, we must keep in mind that we are talking about a radioactivity-concentration range where the

actual physical amount of the drug, which is carrying three levels and very small, minute physical amounts of FDG, isn't really different. It is the amount of radioactivity as the strength, as it is defined, and so it is inappropriate to set that standard in dealing with the definition of strength with a PET radiopharmaceutical especially FDG.

It might be appropriate when there is a PET pharmaceutical that has pharmacological impact or potential to elicit pharmacological response, but not with FDG.

MR. KUHS: It is only the radioactivity that changes in the strength. The molecular composition stays the same. The concentration, by definition, is the amount of radioactivity per unit volume, and when typically, you are talking about concentration, you are talking about different molecular concentrations. That stays the same. It's the radioactivity that changes.

So, a specific concentration shouldn't be an issue in determining bioequivalence or bioavailability.

MS. AXELRAD: I think what we are trying to do here is explain that we have run across, you know, we have been looking at all the different requirements that are in our existing regulations and trying to figure out how they would apply. We are sort of trying to give you an overview of what we see and really to identify the problems we recognize that there are issues associated with this.

So, basically, let's go through what the requirements are and then we can get some comments on what problems those might pose that we can look at.

MR. HUNT: Continuing on to the ammonia N 13, there is no approved product at this time, however, the agency has, as you are aware, gone through and looked at the literature. There has been a review that was prepared that addresses this, and the thinking is that the information that is available via this review process that has gone on internally would be the basis a firm or sponsor could cite from the Federal Register notice where this will, in the future, be referenced.

So, that would meet your in vivo requirement. It would be based upon information that has been already reviewed in the agency and found to be acceptable.

Once the first NDA is approved, then, that puts us into the mode where you can get approval of the ANDA, again showing you have got an approved product, all you have to show is that your product is similar or identical to the reference listed drug.

Again we are dealing with a one-synthesis process and again you have to meet the CMC limits that would be set based on the reference listed drug. So, again, you can get away with a waiver and not needing to do an in vivo type study, and even in the first case, the information that is

in the literature has been found to be acceptable to satisfy that need.

Lastly, is the FDG. I have two scenarios here, but it sounds like the last one is not really relevant because it doesn't appear that the electrophilic procedure is being used here in the U.S., so again, that falls into the former scenario of a waiver, again, that, in fact, a reference listed drug can be established and which is available, and that can information can be disseminated, and then you just have to show that you meet the CMC specs and you are using the same synthesis procedure.

DR. BARRIO: Let me ask you a question about sodium fluoride. Let's go back to this. The original synthesis or rather nuclear reagent being used when large cyclotrons were available, there was, of course, the deuteron neon reaction.

The one that we normally use right now with the smaller cyclotrons being used is the O 18, maybe O 18, mostly O 18 water. What you are trying to say is that you like to demonstrate that you have the two-synthesis procedures, the one that was done before, the deuteron, and the one that is done right now, that the product has the same biological properties.

MR. HUNT: I hope I am correct on this. If you can show that what is made, and if they fall within the CMC

limits that are set by the agency, you can meet those, then, there is probably not a problem unless there is another impurity or something that is formed that we would not expect to see.

DR. KASLIWAL: I think if both the methods are no carrier methods, then, they are pretty much deemed to be the same.

DR. HOUN: I think why we brought this up is just to say that in terms of biopharmaceutic requirements for FDG, ammonia, and sodium fluoride, we are going to be handling it this way, but certainly if new PET drugs are developed, then, the bioavailability, bioequivalence issues come into play, and we would just remind the community that these are other requirements.

MR. SWANSON: I am sorry, I didn't understand that. Doesn't bioequivalency come into play when you submit an ANDA? So, don't these waivers have to apply to equivalency to whatever we grant 505(b) status to or whatever currently has an NDA, is that not correct?

MS. AXELRAD: Bioavailability requirements apply to NDAs; bioequivalence requirements apply to ANDAs, Abbreviated New Drug Applications. Basically, if somebody comes in with a new NDA, maybe not based on the literature, but based on regular clinical studies, there would be certain bioavailability requirements, and then is

subsequently, a generic comes in to the reference listed drug, then, it would come under--usually, it would get a waiver if it's a parenteral kind of a product, but we want you to be aware of what the regulations are.

MR. SWANSON: But then it seems like we have got certain problems now because, as was pointed out, our current NDA FDG probably doesn't represent what a lot of the syntheses are going to be, the same concentration, et cetera.

Our current sodium fluoride approval doesn't represent what is being done out there, and we don't have one, so it seems to me like we are going to end up having to submit--are we going to have to submit multiple NDAs at different concentrations in order to make this work?

What if my PET center is making it at 40 millicuries per milliliter, and they are making it at 100 millicuries per milliliter, and if I want to go the ANDA route, then, I am going to have to tie together with an NDA that is doing that 40 millicuries per milliliter, right?

DR. KASLIWAL: One is the strength, has to be within the strength range, so that is one aspect for ANDA. The other is the composition, if your composition changes, then under certain circumstances, some things are allowed in ANDA, other things are not allowed in ANDA.

MS. AXELRAD: But that is why the (b)(2) route, I

think is available. If you can't show that you are the same as a reference listed drug, then, you can't come in as a generic, but you can come in as a (b)(2).

In this case where all the clinical safety and efficacy data is based on the literature anyway for the three drugs that we are talking about here, there is not a huge difference between a (b)(2) and a (j). It just doesn't really matter that much.

You just have to be aware that if you are going for a (j) and you are going for the sameness, you know, trying to show sameness, then, you have to be aware of the criteria for sameness and see if you are the same. Otherwise, you come in as a (b)(2), and would address the differences.

DR. KASLIWAL: I also just want to clarify when I say composition, we are not talking about impurities that are present. Impurities, you can control. Composition is the active and the inactive ingredients.

MS. AXELRAD: You can sort of mull over, and I would like to move on and mention another little issue, pediatrics. Dr. Love is going to tell you about the requirements. You are probably aware of the Pediatric Rule, or may or may not be aware. We published a final rule on pediatrics. It deals with pediatric studies for drugs, and requires new applicants to address that in a certain way.

Dr. Love is going to summarize that and tell you again how we are going to try and deal with in the PET context.

Pediatric Rule

DR. LOVE: The agency has been concerned about the need for pediatric labeling, as Jane was just saying, and in December 1998, there were regulations published under 314.55 that talk about required pediatric studies for new drugs, new indications, new dosage forms, and the like, and it specifically related to the drug and the indication particularly.

That regulation identifies the fact that there are methods for dealing with this, there can be deferrals, again waivers, full or partial waivers. Those can be initiated either at the request of the sponsor or on the agency's own initiative, and we would look at such things as whether or not the indication is relevant to pediatrics, whether or not the number of pediatric patients that might receive a particular drug for a particular indication is appropriate, the safety of the product, and whether or not it is practical or impractical to do pediatric studies.

Also, in that FR notice, there is a list of indications or diseases for which the agency is expected to or apt to provide a waiver.

So, what we have done is look at these particular drugs that we are considering for this FR notice - FDG,

sodium fluoride, as have been mentioned, and ammonia, and looked at the indications that were discussed at the MIDAG meeting and considered where these drugs and indications would fall in this format.

One of the listed indications in the preamble to the FR notice is atherosclerosis. So, we have looked at the fact that the FDG indication for hibernating myocardium and the indication for ammonia for myocardial perfusion are certainly associated with that, and we feel that we would be able to waive any requirement for those two drugs.

We are taking that information to our Pediatric Committee in the agency that looks at all of this, and will be discussing it with them in two weeks, but that is our expectation at this point in time.

As far as FDG epilepsy, that is already labeled for pediatric use, so that is not a concern.

The other drugs and indications for which we are seeking some information at this point happen to be the FDG for oncology, we certainly expect that it would be used in pediatrics, and the FDG for bone imaging, again, that would be used in pediatrics--I am sorry, sodium fluoride for bone imaging.

What we are doing at this point is seeking information from Oak Ridge and also contacting NIH looking for dosimetry information on these uses, and considering

just putting that information in the labeling and trying to address it from that standpoint.

Where we are running into a little bit of a challenge is finding information on sodium fluoride since that is an old product, and we are looking for information on sodium fluoride in the pediatric population. We are still seeking it from the two sources that I have identified, but also if you have some other information that you could provide to us, that would be helpful. I would also like to get your comments on whether or not you think dosimetry information would even be the appropriate way to go in trying to finalize the labeling for the pediatric population for these two drugs and indications.

DR. BARRIO: But when you are looking for dosimetry information, you mean in children or in adults?

DR. LOVE: Pediatric population specifically, which in the regulations is defined as under 16. Normally, what we do when we are looking at a pediatric population is think more specifically about which pediatric age group is apt to function like the adult population and where you might see differences, so for bone imaging, it would be issues where there is epiphyseal closure has not occurred or where there is a rapid growth spurt or something, and what is happening in that population.

If it's FDG, it may be an issue of whether or not

certain tumors may metabolize the product in a different way in a pediatric population, something that is more specific to pediatrics, or perhaps where the metabolic process on the basis of age may be different.

If those things are not issues, then, we wouldn't worry about them, but that is the general approach we take to thinking through the issue, but specifically, we are looking at dosimetry, probably in a younger age population or smaller body surface size population, not so much the 16-year-olds that are comparable to adults.

MR. SWANSON: Could you summarize for us what the pediatric regulations say, do they actually mandate that industry must do pediatric studies? I thought that there was a series of incentives associated with it.

DR. LOVE: What you are talking about there is the exclusivity process. The Pediatric Rule itself does require pediatric studies for new drugs, new indications, new dosage forms, and the like, and it says the information is required, but the manufacturers, the sponsors can identify situations in which it may not be relevant, and that is when the waivers come into play.

So, as I was mentioning earlier, if an indication is not relevant, if it is a very small population, an orphan indication, that sort of thing, where it is either not wise, unsafe, or impractical to study, but we would need

information that showed that it is impractical.

What we are trying to do is do this across the board and address this up-front. This is not going to be an issue for each individual site to address. This is something that we would like to take care of in the FR notice on safety and effectiveness of these particular drugs and indications.

Our goal here is to also along with all the other notices that would be coming out is to actually publish the labeling, and the labeling would already contain the statement for pediatrics, so this would be done ahead of time.

DR. HUNG: Dr. Love, did I hear you say that you will use body surface to adjust a dosage for pediatric patients?

DR. LOVE: No. I am saying that those would be the kinds of things we would think of in general for pediatrics when we are looking at it, not specifically for--

DR. HUNG: So, you don't have any specific method for adjusting the dosage?

DR. LOVE: There are a number of different approaches and algorithms that can be used to adjust dosing. I think again we look at the specific drug and its mechanism of action and what is taking place. So, that was more of a general comment.

DR. CONTI: I think I said this last time, that dosimetry I think is the key issue. There are pages of ways to calculate this for pediatrics, and it is done routinely for radiopharmaceuticals, such as a technetium bone scan. It is very traditional to adjust the pediatric doses. There are standard ways of doing that.

I would also note to you that since you have already put FDG, according to your label, in children with epilepsy, that since the injected dose is identical whether you are doing an oncology study, epilepsy, or a heart study, that you can just dismiss that now as equivalent if you are using dosimetry per se as the criteria. So, it is done.

DR. HOUN: The label doesn't have, I guess, the information on how much radiation is received to the critical organ for kids. Is that something the label should have or not?

DR. CONTI: It is going to be the same thing as in adults. The biodistribution is essentially identical in an adult. The only difference is going to be the total amount of activity that you are injecting and what that activity is going to expose the critical organs to, which in most cases is the bladder for most of these drugs.

DR. LOVE: And certainly we thought about that particularly for FDG and wondered what is the relationship. One of the key issues in the Pediatric Rule is the

indication, so the issue there is not just the safety in terms of the elimination through the bladder, but also are we going to get a different biodistribution pattern on the basis of disease.

If what you are talking about is true, then, what we simply need are some data to try to support it from administrative record perspective, but I understand what you are saying.

DR. CONTI: I think what I am telling you is I don't think you are going to get it because the only alteration in distribution is going to be in a child with a cancer, and you are going to see uptake in that cancer as opposed to it not being in the cancer.

It is essentially the uptake in the heart, the uptake in the brain, and the normal organs are going to be identical across the board, and I would venture to say that there is probably an insignificant change in dosimetry irrespective of whether they have a cancer or not to the normal organs.

DR. LOVE: What about sodium fluoride in pediatrics--

DR. CONTI: Again, I mean you can use the technetium bone scanning as a means of calculating the same biodistribution and adjusting it exactly the same way as an MDP dose is adjusted, because again it is just a matter of

the total activity that is going to change, not the biodistribution in an adult versus a child.

I mean you are going to see more uptake in the epiphyses just as you would see in a technetium bone scan. So, again, it is the same issue, it is just a matter of adjusting the dose according to the standard calculations.

The only thing I would add to this is that you are not looking at ammonia for the pediatrics, is that--

DR. LOVE: We were considering waiving it because of the indication, atherosclerosis. We actually had data presented at the MIDAG on dosimetry that went down to the age of the ones we actually have some information on.

DR. CONTI: There is little reason to do it for atherosclerosis in children.

DR. LOVE: That is the basis of the waiver.

DR. CONTI: But there are indications, though, in children that would require that you use this drug.

DR. HOUN: Not the one that was reviewed in the literature. If you want to come with a supplement to that--

MS. AXELRAD: You might have to do a study.

DR. CONTI: For coronary artery disease?

DR. HOUN: Everything was looked in, in people with angiography as a gold standard with coronary artery disease.

DR. CONTI: What about Kawasaki's disease, for

example?

DR. HOUN: Not one article had that, not the ones that were reviewed, that met the standard for prospective.

DR. CONTI: Okay.

MS. AXELRAD: If you want to come in and add that indication to the label, you might have to do a study in kids. That is basically what is going to happen.

DR. CONTI: Okay.

User Fees

MS. AXELRAD: The last issue on the agenda for today is user fees. Again, what we want to do is try and address this in an overall fashion in a Federal Register notice. We are examining the possibility of giving a waiver of the application user fees, which I think are going to be the biggest issue. It is under the barrier to innovation provisions under the user fee law that provides that we can give a waiver for anything that is a barrier to innovation based on insufficient resources or other circumstances.

What we are looking at is whether the provisions of FDAMA that tell us to specially regulate PET facilities and to deal with them in a special way, and the equities of the situation in that whoever happens to come in first would happen to pay an application fee, but once the first (b)(2) application is approved, nobody else would have to pay.

It seems sort of unfair that it is just an

accident of whoever steps forward and wants to be first, so it is sort of based on that sort of combination of circumstances, as well as the fact that there isn't going to be any clinical safety and efficacy data in the applications, it is all based on the literature, literature that we ourselves have already reviewed.

We are going to try and see if it would justify a blanket waiver of application fees, and we would try and address that in the Federal Register notice. Once two products are approved, no one pays any--well, ANDAs don't pay any fees anyway, they don't application fees or any other kind of user fee, and really application fees is what the issue is here.

So, I think we can solve that problem if we can determine how to justify that. Again, we think this is a very unique situation, and we are basing it on the sort of uniqueness of this.

That is hopefully where we are going to go on that. Again, it will be addressing it in there. We will let you know if there is some change in that.

DR. HUNG: Could I make a comment? This is Joe Hung from Mayo Clinic.

I know that in the past, collecting the user fee has been very successful in cutting down the review process for the new drug application. By not collecting this user

fee for the PET new drug application, can we anticipate that this will not affect the review process, and how are you going to cope with the inspection process without the additional fund from this user fee, collecting from the users?

MS. AXELRAD: Well, we would love to have somebody voluntarily pay it. We would really like to have the first application and each of these areas pay the fee. You know, we spend quite an amount of our agency resources on this whole project, but we can say that if you do get a waiver, you get the same review, and you are subject to the same standards in terms of timeliness of review whether the fee is waived or the fee isn't waived basically.

I think that covers all the issues that we have. I think we have covered an awful lot of ground today, sort of several steps forward and much more to go, it seems like, but I guess we will go back and try and absorb everything that we got today in terms of feedback.

We will look forward to getting your written comments on all these documents by the 13th, and we will try and revise the documents and see where we go next, after we have had a chance to go over the record.

Thank you very much.

[Whereupon, at 5:50 p.m., the meeting was adjourned.]

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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